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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/755,747	01/05/2001	Anthony J. Brookes	78104.017	3891

7590 03/01/2004

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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 03/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/755,747	BROOKES, ANTHONY J.	
	Examiner	Art Unit	
	Jeffrey Fredman	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *January 13, 2004* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-18,20-31,33-44,46-52 and 67-76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-18,20-31,33-44,46-52 and 67-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 13, 2004 has been entered.

Status

2. Claims 1-5, 7-18, 20-31, 33-44, 46-52, and 67-76 are pending.

Claims 1-5, 7-18, 20-31, 33-44, 46-52, and 67-76 are rejected.

Claim Rejections - 35 USC § 112

3. Claims 1-5, 7-18, 20-31, 33-44, 46-52, and 67-76 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As MPEP 2163.06 notes " If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

The amendment to include the term "monolayer" is new matter. The specification of the instant application was wordsearched, both by an optical character recognition of the specification in the computer version of the application as well as by a word search of the published application. The word "monolayer" as well as the broader term "layer" were both searched (including plurals) and no basis was found for these terms. The response confines itself to the bare statement that "no new matter has been added by the amendments or new claims (see page 14 of response)" but no specific support for the term "monolayer" is identified in the response. Therefore, in the absence of any identified support for the term, the claims are rejected as containing new matter.

Response to Declaration regarding 112, First paragraph

4. The Declaration under 37 CFR 1.132 filed January 13, 2004 is insufficient to overcome the rejection of claims 1-5, 7-18, 20-31, 33-44, 46-52, and 67-76 based upon 35 U.S.C. 112, first paragraph as set forth in the last Office action because:

The Declarant, Dr. Pavel Strohner states that DNA attached to a streptavidin monolayer will inevitably form a superimposed DNA monolayer. This statement is based on both claim interpretations that are not found persuasive and which are not in accord with the complete evidence of record now presented. The claim states "a monolayer of single DNA strands." The claim does not recite a monolayer of streptavidin. As a note, the Declarant's patent does not refer to monolayers either.

Jordan et al (Anal. Chem. (1997) 69 :4939-4947) teaches that the attachment of DNA need not result in a monolayer. This is most clearly demonstrated in table 1, where the attached DNAs clearly form bi and trilayers on the solid support and in figure

1 where multiple layers are present. So that while DNA may form a monolayer on the array, it may also form multilayer structures as well. Therefore, a reliance by the applicant on inherency is not well founded, since it is not inherently true that DNA will form only monolayers on the array.

Attachment of the PCR products to the solid support will not necessarily and inherently result in monolayers of DNA because interactions between the DNA molecules will permit formation of multilayer structures such as those of Jordan. As table 1 of Jordan clearly shows, the DNA can interact to form dendrimers which are not monolayers. While monolayers may certainly result under some circumstances with some DNA sources, other DNA sources will yield multilayer molecules.

Response to Arguments – New matter Rejection

5. Applicant's arguments filed January 13, 2004 have been fully considered but they are not persuasive.

Applicant correctly states the law regarding the issue of support for new limitations where the specification lack ipsis verbis support. Here, there is no question or argument from Applicant that the specification is entirely silent on the word "monolayer", that this word does not appear in the specification, and that the only possible route to find support is to provide evidence, such as the declaration rebutted above, which makes the term "monolayer" inherent in the 2-D hybridization system using streptavidin biotin. As noted in response to the declaration above, this term is NOT inherent in streptavidin interactions with DNA. Jordan et al demonstrate that such hybridization systems can form multiple layers of DNA, and need not necessarily result

in DNA monolayers. In fact, figure 1 of Peluso, cited by Applicant, does not support the conclusion that attachment is inherently limited to monolayers. Peluso simply provides an example where monolayers were formed.

Attachment of the PCR products to the solid support will not necessarily and inherently result in monolayers of DNA because interactions between the DNA molecules will permit formation of multilayer structures such as those of Jordan. As table 1 of Jordan clearly shows, the DNA can interact to form dendrimers which are not monolayers. While monolayers may certainly result under some circumstances with some DNA sources, other DNA sources will yield multilayer molecules. So the argument by Applicant that the result is the inherent and necessary result is not found persuasive and the rejection is maintained. For the same reasons, priority is not granted to the parent applications.

Priority

6. The current claims do not receive priority to the parent application GB 9821989.2 as well as PCT/GB99/03329 because those specifications do not provide descriptive support for monolayers. Therefore, prior art as of the instant filing date is applicable to the current claims.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-5, 8, 10-18, 21, 23-31, 34, 36-44, 47, 49-52, 67-71, 73, 74, and 76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stimpson et al (Proc. Natl. Acad. Sci. (1995) 92:6379-6383) in view of Wittwer (U.S. Patent 6,174,670).

Stimpson teaches a method of detecting DNA variation by monitoring the formation or dissociation of a of a complex (see abstract which states that "single base discrimination is facile") consisting of:

(a) a single strand of a DNA sequence (here the 15 mer oligonucleotide are attached to a glass solid support which is a monolayer of the nucleic acids, since each is directly attached to the glass support itself and not some three dimensional structure; see page 6380, column 1, for example),

(b) an oligonucleotide specific for the single stranded DNA sequence specific for one allele of the variation and capable of hybridizing to the single strand (a) to form a duplex (see the biotinylated complementary sequences, table 1 and page 6380-81, subheading "Hybridization and staining for wave guide")

(c) a marker detection of the duplex structure of (a) plus (b) which forms a complex with the said duplex (here the selenium label, see page 6381, figure 1, for example),

which method comprises:

(1) continually measuring an output signal indicative of the duplex formed from the strand (a) and probe (b) (see page 6382, figure 3) and

(2) recording the conditions at which a change in reaction output signal occurs which is attributable to formation or dissociation of the complex and is thereby correlated with the strength with which the probe (b) has hybridized to the single strand (a) (see page 6383, table 3, where the temperature at which the single base mismatch changes the signal).

Stimpson further teaches formation of two or more complexes, each with a probe specific for a different allele of the variaition, and observing their respective denaturing or annealing conditions to distinguish alleles of the variation (see page 6382, figure 3, where two oligos, 23B and 24B are simultaneously tested).

Stimpson does not teach the use of a marker which is duplex specific in the analysis.

Wittwer et al teaches a method of detecting DNA variation by monitoring the formation or dissociation of a complex (abstract) consisting of:

(a) a single strand of a DNA sequence (here denatured genomic DNA (column 9, line 21) and/or denatured amplified PCR products, including an 81 basepair cystic fibrosis gene product (column 40, lines 58-67)) as well as many longer PCR products such as the 536 base pair b-globin sequence (column 47, line 24),

(b) an oligonucleotide specific for the single stranded DNA sequence (here either the primers used in PCR (column 41, lines 1-20) or pairs of fluorescently labeled oligonucleotide probes (column 9, lines 27-37)),

(c) a marker specific for the duplex structure of (a) plus (b) which forms a complex with the said duplex and reacts uniquely when interacting within the duplex (here either SYBR green, (see column 40, line 65) or the fluorescence resonance energy transfer pair of labels, which differentially fluoresce when in duplex or single stranded states (column 9, lines 27-37)),

which method comprises:

(1) continually measuring an output signal indicative of interaction of the marker with duplex formed from the strand (a) and probe (b) (see column 9, lines 50-55 or column 41, lines 14-17 and figure 43) and

(2) recording the conditions at which a change in reaction output signal occurs which is attributable to formation or dissociation of the complex and is thereby correlated with the strength with which the probe (b) has hybridized to the single strand (a) (see page column 9, lines 55-59 or column 41, lines 14-17 and figure 43).

Column 14 details a similar assay for differentiating the Factor V Leiden mutation. Column 46 teaches the use of two or more complexes of the kind defined, each with a probe specific for a different allele of the mutation which multiple detection probes are distinguished by the different melting peaks (see column 46, lines 49-61).

Wittwer further teaches measurement of the annealing based upon the first or second derivatives of the fluorescent melting curves (column 12 and columns 23-26) and expressly discusses measurement of the second order rate constant (see column 12).

Wittwer expressly teaches with regard to claims 67-70 that "The melting curves are easiest to visualize by plotting the negative derivative of fluorescence with respect to temperature vs temperature (-dF/dT vs T) (column 45, lines 10-14)". Thus, with regard to the negative derivative of the fluorescent measurement, Wittwer is teaching determining the presence of a peak. Wittwer is clearly showing the presence of peaks in figure 46 B, where the homozygous and heterozygous (termed match and mismatch in the claim) are separately identified using the negative derivative data analysis method.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the markers of Wittwer in the mutation detection method of Stimpson since Wittwer states "SYBR™ Green I is a preferred double strand specific dye for fluorescence monitoring of PCR, primarily because of superior sensitivity, arising from greater discrimination between double stranded and single stranded nucleic acid. SYBR™ Green I can be used in any amplification and is inexpensive. In addition, product specificity can be obtained by analysis of melting curves, as will be described momentarily (column 23, lines 9-16)". Thus, an ordinary practitioner would have been motivated to use SYBR™ Green I in the melting curve analytical method of Stimpson since Wittwer teaches that this intercalator is superior in

sensitivity, is useful in the particular assay employed by Stimpson since the waveguides would detect the fluorescent label and is inexpensive.

9. Claims 1-5, 7, 8, 10-18, 20, 21, 23-31, 33, 34, 36-44, 46, 47, 49-52 and 67-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stimpson et al (Proc. Natl. Acad. Sci. (1995) 92:6379-6383) in view of Wittwer (U.S. Patent 6,174,670) and further in view of Heller et al (U.S. Patent 6,048,690).

Stimpson in view of Wittwer teach the limitations of claims 1-5, 8, 10-18, 21, 23-31, 34, 36-44, 47, 49-52, 67-71, 73, 74, and 76 as discussed above. Stimpson in view of Wittwer do not teach immobilization of the oligonucleotide using biotin-streptavidin.

Heller teaches immobilization of oligonucleotides to arrays using biotin-streptavidin for nucleic acid detection assays (column 16, lines 62-67).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the method of Heller in the detection method of Stimpson in view of Wittwer since Heller states "In this example, the first probe (a capture/quencher probe sequence) has two terminal functional groups, a 5'-terminal biotin group which allows the probe to be immobilized to the surface (permeation layer) of a microlocation test site on an active DNA chip or other hybridization device." (column 16, lines 62-67). An ordinary practitioner would have been motivated to use the biotin capture method in order to permit immobilization of probes to desired microlocations of DNA chips for the analytical method. Also, an ordinary practitioner would be motivated to select a known equivalent of the method of Stimpson for

attachment of the nucleic acids to the array as Stimpson teaches biotin capture methods (see page 6380, column 2).

10. Claims 1-6, 8-19, 21-32, 34-45, 47-52, 67-71, 73, 74 and 76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stimpson et al (Proc. Natl. Acad. Sci. (1995) 92:6379-6383) in view of Wittwer (U.S. Patent 6,174,670) and further in view of Konrad et al (U.S. Patent 5,789,167).

Stimpson in view of Wittwer teach the limitations of claims 1-5, 8, 10-18, 21, 23-31, 34, 36-44, 47, 49-52, 67-71, 73, 74, and 76 as discussed above. Stimpson in view of Wittwer do not teach the use of Hepes buffer in hybridization.

Konrad teaches that " The conditions for hybridization of oligonucleotide sequences are well known. Generally, the hybridization step is either performed in a buffered aqueous salt solution at high temperature or in the presence of formamide at lower temperature. The aqueous, high temperature procedure is typically carried out in a Tris buffer, such as 0.3M NaCl, 20 mM Tris -HCl, pH 6.8, at 67.degree. C. Other buffering systems such as hepes or glycine-NaOH and potassium phosphate buffers can be used. (column 14, lines 59-67)".

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the Hepes buffer of Konrad in the detection method of Stimpson in view of Wittwer since Konrad expressly teaches that Hepes buffer is an equivalent buffer for use in hybridization reactions.

Response to Declaration regarding 103 rejection

11. The Declaration under 37 CFR 1.132 filed January 13, 2004 is insufficient to overcome the rejection of claims 1-5, 7-18, 20-31, 33-44, 46-52, and 67-76 based upon 35 U.S.C. 103 as set forth in the last Office action because:

The Declarant, Dr. John Baldeschwieler states that Stimpson would not provide sufficiently strong fluorescent signals for "sub-second" detection methods and that one would have been motivated to use 3-D gels for this methodology. This is not found persuasive for several reasons. First, the argument is not correlated with the claim. There is no requirement in any of the current claims for a "sub-second" detection. So the fundamental argument and reasoning underlying the Declaration are not relevant to the invention as claimed. Second, the argument is not found to be consistent with the prior art. It was routine, as of the filing date of Stimpson, to detect fluorescence signals from hybridization reactions on solid supports. As demonstrated by both Stimpson and Heller, both patents cited and of record, 2-D supports were capable of detecting fluorescent changes due to specific hybridization of DNA molecules. These are representative of an abundant area of prior art, with Heller alone having many patents in this area showing such detections. In fact, as far back as a patent issued in 1989, Heller taught that ONE second was sufficient time to analyse the fluorescent signal (see U.S. Patent 4,824,776, column 9, line 18, "The fluorescent signal from each sample spot was counted (EG&G photon counting System) for one second."). Thus, even as of 1985, the filing date of this Heller patent, single second counting was capable of being

performed. So the declaration statement that such detection would not function is not in accord with the prior art.

Response to Arguments regarding 103 rejection

12. Applicant's arguments filed January 13, 2004 have been fully considered but they are not persuasive.

Applicant first argues that Stimpson teaches away from the use of the Wittwer detection system. Applicant also makes the argument that detection is slow. As an initial point, these arguments are not addressed to the claims. There are no limitations in the claims regarding the speed of hybridization. Second, MPEP 2123 notes "Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments." Here, Stimpson unquestionably has a broader disclosure than the specific methods of reading the DNA chip, but indicates that it's fluorescence is lower than that of the 3-D system. That is not a teaching away from the use of the nonpreferred embodiment but simply a teaching towards the 3-D system.

When Applicant argues that melting curves cannot be produced using DNA on a solid surface using fluorescent detection in real time, this statement is simply not correct. Walt et al (U.S. Patent 6,406,845) filed May 5, 1997, demonstrates a DNA melting curve on a 2-D system is functional as shown in figure 29. So the art was capable of performing such melting curves prior to the instant filing. The combination of Stimpson with the more sensitive SYBR-green dye of Wittwer would overcome the low fluorescence problems identified by Stimpson.

Finally, the modification to use Wittwer does not render the method of Stimpson unsatisfactory, as Applicant argues, but rather makes it more desirable. An ordinary practitioner would have been motivated to apply the specific and sensitive detection method of Wittwer to improve the specificity and sensitivity of the Stimpson method.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Here, Applicant applies a piecemeal analysis by saying that if one wanted to perform the method of Wittwer, one would use Wittwer, while if one wanted to detect variation, one would use Stimpson. It is the combination of these teachings that renders the claims obvious, and particularly the teaching by Wittwer that Sybr Green is a very sensitive detection molecule.

In fact, the improved sensitivity of SYBR green addresses the other issues earlier raised by Applicant, since the combination would improve the sensitivity to a level permissive of 2-D detection of the melting curves and since Stimpson recognizes a problem, less fluorescence than desired, and Wittwer provides a solution, the use of the sensitive dye SYBR green, that alone provides motivation to combine these references.

Applicant then argues the further rejection over Heller by arguing that Heller is performing a different method. Heller provides evidence that the use of streptavidin-biotin interactions is routine in the art and motivates their use in any art recognized method.

The remaining rejections are also maintained as Applicant relies upon overcoming the previous rejections to overcome this rejection.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey Fredman
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Art Unit 1634